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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUANG, GIGI GEORGIANA	

ART UNIT	PAPER NUMBER
1612	

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02/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,154	KLOBCAR ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/4/2008; 11/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The response filed November 19, 2008 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claims 13-14 have been amended.

2. Claims 13-17 are pending in the case.

3. Claims 13-17 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn moot.

Information Disclosure Statement

6. The information disclosure statement filed September 4, 2008 and the duplicate of the same IDS filed on November 19, 2008 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because there are several references listed without translations for consideration, they are indicated on the IDS. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a). It is noted that EP 1338951 has been corrected.

New Grounds of Rejection

Due to the amendments to the claims, the following rejections are applied:

7. Claim 13-14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guez et al. (WO 99/25374) in view of Eyjolfsson (WO 03/059388).

It is noted that Guez et al (U.S. Pat. 6653336) will be used as the translation for Guez et al. (WO 99/25374) and all references will be to the U.S. Pat.

Guez et al. teaches the combination of an angiotensin-converting enzyme inhibitor (ACE or CEI) and a diuretic in a pharmaceutical composition. Guez teaches the benefits of the combination and the preferred CEI particularly is perindopril and its salts. The preferred diuretic is indapamide and hydrochlorothiazide and their salts, more particularly indapamide. Examples teach the combination of perindopril and indapamide in pharmaceutical compositions with excipients including microcrystalline cellulose. Guez teaches the inclusion of excipients, binders, diluents, stabilizing agents, and other desirable components (Abstract, Col. 2 line 55-62, Col. 3 line 11-Col. 4 line 50). It is known in the art that microcrystalline cellulose is a moisture control agent and the commercially available products (such as Avicel®PH-101) generally have moisture contents of less than 5% (see Signet sheets). Guez also teaches several composition forms including instantaneous and delayed release.

Guez et al. does not expressly teach the use of a carbonate at a molar ratio of 1 to 0.1-0.9 or the ratio of 1 to 0.50-0.83 for perindopril to inorganic carbonate. Guez does teach the inclusion of excipients such as stabilizing agents in the formulation.

Eyjolfsson teaches the inclusion of components including of carbonates, particularly alkali or alkaline-earth metal carbonates produce useful and stable ACE inhibitor formulations. The ACE inhibitors taught include perindopril and the combination of diuretics. Eyjolfsson teaches a preferred embodiment of the amount of carbonate to at least the equivalent of the active. However, the general teaching of Eyjolfsson is to the inclusion of carbonates for the production of stable ACE inhibitor formulations and claims a composition with an ACE inhibitor including perindopril, at 0.5-50wt.%, and the alkali or alkaline earth metal carbonate at 5-90% encompassing ratios in the preferred embodiment such as 1:1 and ratios beyond the preferred embodiment, such as 1:0.5 and 1:0.9 (see document, specifically Abstract, Page 2 line 5-16, page 3 line 24-25, Page 4 line 10-15, Claims 1-2, 4, 11).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to include carbonates and optimize the molar ratio to the ACE inhibitor, as suggested by Eyjolfsson, and produce the instant invention.

It would have been obvious at the time of the invention to incorporate components to increase stabilization of a formulation as taught by Guez; with components such as the carbonates taught by Eyjolfsson for ACE inhibitors like perindopril. Although Eyjolfsson teaches a preferred embodiment wherein the amount of carbonate to at least the equivalent of the active, the teaching as a whole is to the inclusion of carbonates for the improved stabilization of ACE inhibitor and it would have been obvious to one of skill in the art to optimize the amount carbonate beyond the preferred range as the general teaching encompasses ratios below 1:1 as presented in

the claims and the specification to affect the amount of stabilization for a pharmaceutical formulation. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation as the adjustment of particular conventional working conditions, such as determining a suitable effective dosage in combination with other component ranges, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan to yield the desired properties in the composition.

One of ordinary skill in the art would have been motivated to do this because combining components that would provide a more stable composition and yield an increasingly effective and desirable product with better shelf life is desirable.

8. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guez et al. (WO 99/25374) in view of Eyjolfsson (WO 03/059388) as applied to claim 13 and 14 above, in view of www.signetchem.com, and further in view of Cooper et al. (U.S. Pat. Publication 2003/0232796).

The teachings of Guez et al. in view of Eyjolfsson are addressed above.

Guez et al. in view of Eyjolfsson do not expressly teach the use of microcrystalline cellulose with a moisture content of 0.3-1.5% by weight. Guez does teach the inclusion of microcrystalline cellulose and the diuretic indapamide. Guez also teaches several composition forms including instantaneous and delayed release.

www.signetchem.com teaches that a number of commercial microcrystalline celluloses with different properties, size, and forms were readily available for purchase

and use in 2002 for one of skill in the art at the time of the invention to produce the product properties desired.

Cooper et al. teaches the use of nanoparticles of active agents with various particle sizes of other actives to obtain immediate-release and controlled-release forms. The actives include cardiovascular agents, cardiac ionotropic agent, diuretic, and antihypertensive agents.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize any commercially available microcrystalline celluloses (e.g. Avicel®PH-112) and to modify the particle size of the drugs, in the composition taught by Guez, as suggested by www.signetchem.com and Cooper, and produce the instant invention.

It would have been obvious at the time of the invention to purchase any appropriate microcrystalline cellulose such as Avicel®PH-112 to use and to modify the composition taught by Guez in view of Eyjolfsson as needed to arrive at a final product with the desired properties. It would have also been obvious to modify the teachings presented by Guez including particle size, to create products with any number of specialized forms and applications (e.g. immediate release, delayed release, etc.) depending the on the drug release profile and form desired which is well within the skill of one in the art.

One of ordinary skill in the art would have been motivated to do this because it is more cost effective to purchase a commercial product than to produce the

microcrystalline cellulose yourself, and the commercial product is desirable as it had consistent properties and uniformity in the mixture. One would have been motivated to modify the components (microcrystalline cellulose, particle size, etc.) to provide a number of materials that would be uniquely suited for the product use desired such as immediate release or controlled release compositions which are modifiable base on the components and/or particle size to yield the desired drug release profile.

Response to Arguments

9. In regards to Applicant's arguments to Guez et al. (WO 99/25374) in view of Eyjolfsson (WO 03/059388), Applicant's arguments filed 11/19/2008 have been fully considered but they are not persuasive. Applicant asserts that the ratio is unexpected and that Eyjolfsson teaches away from the ratio. This is not persuasive as Guez teaches the use of stabilizing agents, Eyjolfsson teaches that incorporation of carbonates (e.g. alkali and alkaline) stabilize ACE inhibitor formulations including perindopril. The general teaching of Eyjolfsson is for the incorporation of these carbonates with ACE inhibitors and the claimed ranges for both these components include ratios above and below 1:1. It is obvious an well within the skill of one in the art to optimize the amounts of the carbonate and inhibitor to arrive at the desired amount of stabilization including the broad ratio of 1 to 0.1-0.9 and 1 to 0.50-0.83 when the general conditions of a claim are disclosed in the prior art. As for unexpected results, the assertion of unexpected result is insufficient when there is no evidence of unexpected result and the general ranges are presented in the general teaching.

Conclusion

10. Claims 13-17 are rejected.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612